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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/700,417	11/29/2000	Tony Kouzarides	620-118	3566

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EXAMINER
CANELLA, KAREN A

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/700,417	Applicant(s) Kouzarides
	Examiner Karen Canella	Art Unit 1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____.

2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☒ Claim(s) *2 and 9* is/are allowed.

6) ☒ Claim(s) *1, 3-8, and 10-18* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). 6
18) ☐ Interview Summary (PTO-413) Paper No(s). _____
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

DETAILED ACTION

1. Acknowledgment is made of applicants election, with traverse, of Group I. The traversal is on the grounds that the instant invention has unity of invention, as the IPER acknowledges novelty of claims 1-20. This has been considered and found persuasive. The restriction requirement of Paper No. 8 is withdrawn.

2. Claim 21 has been canceled. Claims 1-18 are pending and examined on the merits

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1, 3-8 and 10-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1 and 3 recite a method claim comprising parts (a) or (b) or (c) and (d), and it is not clear if part (d) is to be applied to parts (a) and (b) or if part (d) is applied solely to part (c). For purpose of examination, part (d) will be applied to parts (a)- (c).

Claim 1(a) recites: "treating an acetylated E2F polypeptide or peptide". It is not clear from the claim if the "peptide" must also be acetylated. For purpose of examination, the claim will be read as --- treating an acetylated E2F polypeptide or an acetylated E2F peptide---.

Claim 4 recites: " a test compound under conditions in which, in the absence of the test compound being an inhibitor, the first and second substances interact:". It is not clear if the claim encompasses test substances that are inhibitors of the interaction between a P/CAF polypeptide or peptide and an E2F polypeptide or peptide. For purpose of examination, inhibitors will be included in the metes and bounds of claim 4.

Claims 5 and 8 recite: "(iii) oncogenicity of cells, and/or or (iv) induction of apopotosis in cells" and thus is indefinite in the inclusion of and/or. For purpose of examination, the claims will be read as ---(iii) oncogenicity of cells, or (iv) induction of apopotosis in cells---.

Claims 12 and 14 recite, "where said agent is peptidyl, nucleic acid encoding a said agent". It is not clear if the claim embodies peptidyl nucleic acids or peptides and nucleic acids. For purpose of examination, the claim will be read as being drawn to peptides and nucleic acids.

Claim 12 recites, "a method ...comprising providing a said agent, or where said agent is a peptidyl, nucleic acid....to cells to modulate one or more...". Claim 14 recites, " a method comprising use of said agent, or where said agent is peptidyl, nucleic acid encoding said agent, in the manufacture of a medicament for treating a disorder of cell growth". In both claims, the agent which is not a peptidyl, nucleic acid is not linked to an active method step. Thus, claim 12 describes providing said agent and claim 14 describes use of said agent. The claims are drawn to a method of using an agent, but fail to set forth any active, positive steps that define the claimed method.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 15-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

(A)As drawn to pharmaceutical compositions

Claim 11 is drawn to an agent which affects E2F acetylation formulated into a composition including a pharmaceutically acceptable excipient. Claim 14 is drawn to the use of an agent which affects the acetylation of E2F in the manufacture of a medicament for treating a

disorder of cell growth. The specification does not provide an objective evidence that an agent which interferes with the acetylation of E2F could be used in a method of treating a disorder of cell growth. Although it is known in the art that deregulated expression and altered function of genes involved in cell cycle regulation contribute to the pathogenesis of cancer (Hartwell et al, Science, 1994, Vol. 266, pp. 1821-1828), it cannot be anticipated that agents which interfere with the acetylation of E2F could be used in a pharmaceutical composition for the treatment of cell growth disorders. The art teaches that E2F is regulated binding with "pocket proteins" such as the retinoblastoma tumor suppressor protein (Ferreira et al, PNAS, 1998, Vol. 95, pp. 10493-10498) and is responsible for the transcription of genes needed for entry into S phase (Nevins et al, Science, 1992, vol. 258, pp. 424-429). It has been reported that overexpression of E2F in fibroblasts induced premature S-phase entry resulting in apoptosis, and that downregulation of E2F activity leads to resistance to apoptosis (Bargou et al, Journal of Experimental Medicine, 1996, Vol. 183, pp. 1205-1213). Thus, agents, such as peptides which compete with E2F for binding to P/CAF will decrease the acetylation and transcriptional activity of E2F, and increase resistance to apoptosis. The specification has not identified a disease associated with enhanced apoptosis which could benefit by administration of an agent which decreases apoptosis. Further, it appears that the agents are not selective for diseased cells nor would it be expected that the pharmaceutical composition or medicament would act only on diseased cells since E2F occurs ubiquitously. In addition, pharmaceutical compositions must be delivered into the circulation that supplies the diseased tissue or organ and be taken up by the diseased cells at a sufficient concentration and for a sufficient period of time to induce a therapeutic effect. The specification does not teach how to make/use a pharmaceutical composition targeted to tissues or organs undergoing enhanced apoptosis. In addition variables such as biological stability, half-life or clearance from the blood are important parameters in achieving successful treatment. The pharmaceutical composition may be inactivated in vivo before producing a sufficient effect, for example, by degradation, immunological activation or due to an inherently short half life of the

composition. In addition, the composition may not otherwise reach the target because of its inability to penetrate tissues or cells where its activity is to be exerted, or it may be absorbed by fluids, cells and tissues where the composition has no effect, and circulation into the target area may be insufficient to carry the composition and a large enough local concentration may not be established. The specification provides insufficient guidance with regard to these issues and provides no working examples which would provide guidance to one skilled in the art and no evidence has been provided which would allow one of skill in the art to predict the efficacy of using the claimed agents in pharmaceutical compositions or medicaments for the treatment of disease with a reasonable expectation of success. In view of the above, one of skill in the art would be forced into undue experimentation in order to practice the claimed invention.

(B)As drawn to peptide fragments

Claim 15 is drawn to a peptide fragment of E2F or P/CAF of about 40 amino acids or less which modulates the interaction between E2F and P/CAF. Claim 18 is drawn to the isolated nucleic acid encoding the peptide of claim 15. Claim 16 specifically embodies an E2F peptide comprising one or more lysine residues corresponding to those found at positions 117, 120 and 125 in wild-type E2F1. Claim 17 embodies a peptide of 20 amino acids having the characteristic of the peptide of claim 16. The specification teaches that a fragment of E2F1 corresponding to amino acids 89-432 was acetylated by interaction with P/CAF. The specification teaches that other E2F1 deletion proteins corresponding to amino acid residues 380-432, 358-432, 287-432 were not acetylated by P/CAF and therefore acetylation must be occurring between residues 89 and 286 of E2F1. The specification further teaches that the E2F1 lysine residues of 117, 120 and 125 were acetylated by P/CAF. The specification does not teach any peptide fragment which interferers with or modulates this acetylation. It is known in the art that physical interaction between E2F1 and a histone acetylase transcriptional coactivator is complex. For example, Trouche et al (Nucleic Acids Research, 1996, Vol. 24, pp. 4139-4145) teach that three modules of E2F1 interact with the transcriptional coactivator CBP, and that module 3, although required

for CBP binding, is not sufficient for CBP interaction (Trouche et al, page 4143, column 2, lines 24-27). Trouche et al further suggest that additional undisclosed residues within modules 1 and 2, which are not co-linear within E2F1, are required for CBP contact. Thus it can be concluded that a peptide fragment consisting of module 3 would not be able to bind to CBP or to interfere with the binding of E2F with CBP. The instant specification teaches that amino acid residues 89-432 were acetylated by P/CAF. The specification does not demonstrate that a smaller fragment of residues 89-432 would be sufficient to bind P/CAF and would bind P/CAF in preference to E2F1 thus interfering with the acetylation of wild-type E2F. The specification teaches that residues 117, 120 and 125 of wild-type E2F1 are acetylated by P/CAF. Although it can be assumed that residues 117 through 125 contact P/CAF, it cannot be assumed that peptides comprising residues 117 through 125 of E2F1 within a fragment smaller than residues 89-432 of E2F1 will be sufficient to interact with P/CAF and compete with wild-type E2F1 for binding to P/CAF. The specification further teaches that acetyltransferase activity of P/CAF is confined to residues 352-658 of P/CAF. The specification does not teach a fragment of residues 352-658 of P/CAF which could be used to interfere with the binding of E2F to wild-type P/CAF and this fragment cannot be anticipated from the sequence of P/CAF for the reasons set forth from the teaching of Trouche et al. Given the lack of guidance in the specification and the unreliability of predicting the sequence of a peptide which would interact with a histone acetylase and interfere with the binding of E2F, one of skill in the art would be subjected to undue experimentation in order to make the claimed peptides.

Conclusion

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are

unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.
Patent Examiner, Group 1642
January 25, 2002

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